IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **Ranatunge et al**

Application No: **10/608,333** Group Art Unit: **1626**

Filed: **June 30, 2003** Examiner: **T.A. Solola**

For: **Oxime and/or Hydrozone containing Nitrosated and/or Nitrosylated Cyclooxygenase-2 Inhibitors, Compositions and Methods of Uses**

Attorney Docket No: **102258.153 US1**

Commissioner of Patents
PO Box 1450
Alexandria, VA 22313-1450

Petition from Requirement for Restriction under 37 C.F.R. § 1.144

Applicants petition under 37 C.F.R. § 1.144 from the Examiner's final restriction requirement set forth in the Office Action dated February 18, 2005.

I. The Restriction Requirement

On November 19 2004, the Examiner made a twenty five-way restriction requirement of pending claims 1-58. Applicants traversed the Examiner's restriction requirement on December 16, 2004, and provisionally elected Group II, with traverse.

In the office action dated February 18, 2005, the Examiner maintained the twenty five-way restriction requirement. The Examiner only searched and examined the elected species, and refused to extend the search/examination beyond the elected species. In view thereof, the Examiner withdrew from consideration all subject matter that did not read on the elected species.

This Petition is timely filed: Applicants requested reconsideration under 37 C.F.R. § 1.143 and made a provisional election with traverse.

II All the Pending Claims are Related

All the pending claims are related. In particular, pending claims 2-59 all require a compound of Formula (II) that is a **nitrosated and/or nitrosylated cyclooxygenase-2 inhibitor.**

The pending claims, as amended to comply with the restriction requirement for the compounds of Formula (II), are attached hereto as Appendix 1.

The Examiner restricted the invention as follows:

Group I	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula I
Group II	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions Formula II
Group III	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula III
Group IV	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula IV
Group V	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula V
Group VI	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula VI
Group VII	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula VII
Group VIII	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula VIII
Group IX	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula IX
Group X	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula X
Group XI	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula XI
Group XII	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula XII
Group XIII	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula XIII
Group XIV	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula XIV
Group XV	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula XV
Group XVI	Claims 1-2, 14-16, 28-39, 55-57	Compounds and compositions of Formula XVI
Group XVII	Claims 3, 17 and 40	Method of reducing inflammation, pain or fever

Group XVIII	Claims 4-5, 18-19, 41-42	Method of treating GI disorders
Group XIX	Claims 6-8, 20-21, 43-44	Method for facilitating wound healing
Group XX	Claims 8, 22, 45	Method of treating or reversing renal and/or respiratory toxicity
Group XXI	Claims 9-10, 23-24, 46-47	Method of treating disorders resulting from elevated COX-2
Group XXII	Claims 11, 25, 48	Method of treating cancers
Group XXIII	Claims 12, 26, 49	Method of treating central nervous disorders
Group XXIV	Claims 13, 27, 50	Method of inhibiting platelet aggregation
Group XXV	Claims 51-54, 58	Kits for the compounds of Formulas I-XVI

III. Restriction is Not Proper When the Claims are Related

As stated in MPEP §808.02, "[w]here, as disclosed in the application, the several inventions claimed are related, and such related inventions are not patentably distinct as claimed, restriction under 35 U.S.C. § 121 is never proper (MPEP §806.05)."

All the pending claims are related. Thus, the restriction requirement is not proper. Moreover, the Examiner's refusal to extend the search/examination beyond the elected species is not proper. To show that the inventions are distinct, the Examiner must show either that (1) there is a separate classification of the claims; (2) a separate status in the art when they are classifiable together; or (3) a different field of search. *In re Kase*, USPQ2d 1063 (US PTO Director, 2004).

None of these three criteria have been shown with the claims of this application:

If the nitrosated and/or nitrosylated cyclooxygenase-2 inhibitor compounds and compositions of Formula (II) are allowable, then all the kits and methods of use for these compositions would also be allowable. In other words, every pending claim that requires a **nitrosated and/or nitrosylated cyclooxygenase-2 inhibitor compound** would also be allowable. *In re Kase*, USPQ2d 1063 (US PTO Director, 2004).

A search of the prior art for the nitrosated and/or nitrosylated cyclooxygenase-2 inhibitor compounds and compositions of Formula (II) would necessarily encompass a search of the prior art for their methods of use and the kits comprising the compounds and compositions. Thus, the prior art for the nitrosated and/or nitrosylated cyclooxygenase-2 inhibitor compounds and compositions of Formula (II), will also be the same prior art for their methods of use and kits for the compositions comprising the nitrosated and/or nitrosylated cyclooxygenase-2 inhibitor compounds of Formula (II) (i.e., Groups XVII-XXV).

IV. Related Applications

Applicants would like to bring to the attention of the Patent Office U.S. Patent No. 6,649,929, a copy of which is attached hereto. In this issued patent the claims directed to the compounds, compositions and kits of Formula (II) and their methods of use were all examined together. The difference between the claims in U.S. Patent No. 6,649,929 and the present application is that the nitrosated and/or nitrosylated cyclooxygenase-2 inhibitor compounds of Formula (II) in present application must contain at least one oxime group and/or hydrazone group. As the compounds, compositions and kits of Formula (II) and their methods of use were all examined together in U.S. Patent No. 6,649,929, it would not place an undue burden on the Examiner to examine all the pending claims for the compounds of Formula (II) of the present application together. In view of the above, Applicants respectfully submit that the restriction requirement in the present application is improper.

V. Examination of Additional Species

In the office action dated February 18, 2005, the Examiner only search and examined the elected species; refused to extend the search/examination beyond the elected species; and withdrew from consideration subject matter that did not read on the elected species.

Applicants respectfully submit that the pending claims are all directed to the compounds of Formula (II) and fully comply with the Examiner's Restriction Requirement dated November 16, 2004. In response to the restriction requirement Applicant's elected Examiner's Group II, with traverse, drawn to the compounds of Formula (II) and compositions thereof.

Pursuant to MPEP § 803.02, Applicants respectfully request the examination of additional species upon an indication of the allowability of the elected species in claim 1 (new claim 59), 2, 14-16, 28-39 and 55-57. MPEP § 803.02 states that "should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended [to the non-elected species]....The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim".

The Examiner has not cited any prior art for the elected species. The Examiner's refusal to examine any compounds beyond the elected species for claims 1 (now claim 59), 2, 14-16, 28-29, 55-57 in the pending application is improper. As stated in the MPEP, the Examiner must extend the prior art search to encompass the non-elected species (i.e., the compound of Group II).

Additionally, applicants respectfully submit that the Patent Office has failed to properly follow the MPEP guidelines for unity of invention within a Markush-type group. MPEP § 803.02 states (Emphasis added):

> "Broadly unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility"

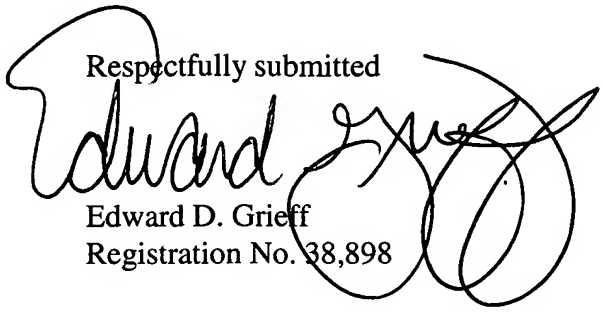
The Examiner failed to appreciate that the compounds of Formula (II) all share a common core (i.e., compounds of Formula (II) that must contain at least one oxime group and/or hydrazone group) and are a recognized class of chemical compounds (i.e., cyclooxygenase-2 inhibitor compounds) and there is an expectation from the knowledge in the art that members of this class (i.e., cyclooxygenase-2 inhibitor compounds) will behave in the same way in the context of the claimed invention.

In view of the above, Applicants respectfully submit that the claims should not be restricted solely to the elected species and respectfully request that the rejoinder and examination of the non-elected species of the compounds of Formula (II) (i.e., Group II).

VI. Conclusion

Applicants respectfully request that the restriction requirement be with drawn, that the examination of claims 1 (now claim 59), 2, 14-16, 28-29, 55-57 be expanded to include the non-elected species of Group II.

Respectfully submitted



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Appendix 1 – Pending Claims as of May 18, 2005

2. A composition comprising the compound of claim 59 and a pharmaceutically acceptable carrier.

3. A method for treating or reducing inflammation, pain or fever in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

4. A method for treating a gastrointestinal disorder, or improving the gastrointestinal properties of a COX-2 inhibitor in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

5. The method of claim 4, wherein the gastrointestinal disorder is an inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a bacterial infection, short-bowel (anastomosis) syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia

6. A method for facilitating wound healing in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

7. The method of claim 6, wherein the wound is an ulcer.

8. A method for treating or reversing renal and/or respiratory toxicity in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

9. A method for treating a disorder resulting from elevated levels of COX-2 in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

10. The method of claim 9, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, a skin-related condition, neoplasia, an inflammatory process in a disease, an ophthalmic disorder, pulmonary inflammation, a central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, a microbial infection, a cardiovascular disorder, a urinary disorder, a urological disorder, endothelial

dysfunction, organ deterioration, tissue deterioration, or activation, adhesion and infiltration of neutrophils at the site of inflammation.

11. The method of claim 10, wherein the neoplasia is a brain cancer, a bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), a basal cell carcinoma, an adenocarcinoma, a gastrointestinal cancer, a lip cancer, a mouth cancer, an esophageal cancer, a small bowel cancer, a stomach cancer, a colon cancer, a liver cancer, a bladder cancer, a pancreas cancer, an ovary cancer, a cervical cancer, a lung cancer, a breast cancer, a skin cancer, a squamus cell cancer, a basal cell cancer, a prostate cancer, a renal cell carcinoma, a cancerous tumor, a growth, a polyp, an adenomatous polyp, a familial adenomatous polyposis or a fibrosis resulting from radiation therapy.

12. The method of claim 10, wherein the central nervous system disorder is cortical dementia, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, or central nervous system damage resulting from stroke, ischemia or trauma.

13. A method for inhibiting platelet aggregation in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

14. The composition of claim 2, further comprising at least one therapeutic agent.

15. The composition of claim 14, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase (5-LO) inhibitor, a leukotriene B_4 receptor antagonist, a leukotriene A_4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H_2 antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a *Helicobacter pylori* inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

16. The composition of claim 15, wherein the nonsteroidal antiinflammatory compound is acetaminophen, aspirin, diclofenac, ibuprofen, ketoprofen or naproxen.

17. A method for treating or reducing inflammation, pain or fever in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 14.

18. A method for treating a gastrointestinal disorder, or improving the gastrointestinal properties of a COX-2 inhibitor in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 14.

19. The method of claim 18, wherein the gastrointestinal disorder is an inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a bacterial infection, short-bowel (anastomosis) syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

20. A method for facilitating wound healing in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 14.

21. The method of claim 20, wherein the wound is an ulcer.

22. A method for treating or reversing renal and/or respiratory toxicity in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 14.

23. A method for treating a disorder resulting from elevated levels of COX-2 in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 14.

24. The method of claim 23, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, a skin-related condition, neoplasia, an inflammatory process in a disease, an ophthalmic disorder, pulmonary inflammation, a central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, a microbial infection, a cardiovascular disorder, a urinary disorder, a urological disorder, endothelial dysfunction, organ deterioration, tissue deterioration, or activation, adhesion and infiltration of neutrophils at the site of inflammation.

25. The method of claim 24, wherein the neoplasia is a brain cancer, a bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), a basal cell carcinoma, an adenocarcinoma, a gastrointestinal cancer, a lip cancer, a mouth cancer, an esophageal cancer, a small bowel cancer, a stomach cancer, a colon cancer, a liver cancer, a bladder cancer, a pancreas cancer, an ovary cancer, a cervical cancer, a lung cancer, a breast cancer, a skin cancer, a squamus cell cancer, a basal cell cancer, a prostate cancer, a renal cell carcinoma, a cancerous tumor, a growth, a polyp, an adenomatous polyp, a familial adenomatous polyposis or a fibrosis resulting from radiation therapy.

26. The method of claim 24, wherein the central nervous system disorder is cortical dementia, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, or central nervous system damage resulting from stroke, ischemia or trauma.

27. A method for inhibiting platelet aggregation in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 14.

28. A composition comprising at least one compound of claim 59 and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

29. The composition of claim 28, further comprising a pharmaceutically acceptable carrier.

30. The composition of claim 28, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

31. The composition of claim 30, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione, or S-nitroso-cysteinyl-glycine.

32. The composition of claim 30, wherein the S-nitrosothiol is:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; or

(iii) H_2N-CH(CO_2H)-(CH_2)$_m$-C(O)NH-CH(CH_2SNO)-C(O)NH-CH_2-CO_2H;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring. a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, an arylsulfonyloxy, a urea, a nitro, -T-Q'-, or –($C(R_g)(R_h)$)$_k$-T-Q' or R_e and R_f taken together are an oxo, a methanthial, a heterocyclic ring, a cycloalkyl group, an oxime, a hydrazone or a bridged cycloalkyl group; Q' is -NO or -NO_2; and T is independently a covalent bond, a carbonyl, an oxygen, -$S(O)_o$- or -$N(R_a)R_i$-, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyloxy, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, -CH_2-C(T-Q')(R_g)(R_h), or -(N_2O_2-)$^-$•M^+, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is -CH_2-C(T-Q')(R_g)(R_h) or -(N_2O_2-)•M^+; then "-T-Q'" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group; and R_g and R_h at each occurrence are independently R_e.

33. The composition of claim 28, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated L-homoarginine, nitrosylated L-homoarginine), citrulline, ornithine, glutamine, lysine, an arginase inhibitor or a nitric oxide mediator.

34. The composition of claim 28, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

(i) a compound that comprises at least one ON-O- or ON-N- group;

(ii) a compound that comprises at least one O_2N-O-, O_2N-N- or O_2N-S- or group;

(iii) a N-oxo-N-nitrosoamine having the formula: $R^{1''}R^{2''}N$-N(O-M^+)-NO, wherein $R^{1''}$ and $R^{2''}$ are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

35. The composition of claim 34, wherein the compound comprising at least one ON-O- or ON-N- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, an ON-O-heterocyclic compound or an ON-N-heterocyclic compound.

36. The composition of claim 34, wherein compound comprising at least one O_2N-O-, O_2N-N- or O_2N-S- group is an O_2N-O-polypeptide, an O_2N-N-polypeptide, an O_2N-S-polypeptide, an O_2N-O-amino acid, O_2N-N-amino acid, O_2N-S-amino acid, an O_2N-O-sugar, an O_2N-N-sugar, O_2N-S-sugar, an O_2N-O-oligonucleotide, an O_2N-N-oligonucleotide, an O_2N-S-oligonucleotide, , a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-S-hydrocarbon, an O_2N-O-heterocyclic compound, an O_2N-N-heterocyclic compound or an O_2N-S-heterocyclic compound.

37. The composition of claim 28, further comprising at least one therapeutic agent.

38. The composition of claim 37, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase (5-LO) inhibitor, a leukotriene B_4

receptor antagonist, a leukotriene A_4 hydrolase inhibitor, a 5-HT agonist, a HMG CoA inhibitor, a H_2 antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a *Helicobacter pylori* inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

39. The composition of claim 38, wherein the nonsteroidal antiinflammatory compound is acetaminophen, aspirin, diclofenac, ibuprofen, ketoprofen or naproxen.

40. A method for treating or reducing inflammation, pain or fever in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 29 or 37.

41. A method for treating a gastrointestinal disorder, or improving the gastrointestinal properties of a COX-2 inhibitor in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 29 or 37.

42. The method of claim 41, wherein the gastrointestinal disorder is an inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a bacterial infection, short-bowel (anastomosis) syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

43. A method for facilitating wound healing in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 29 or 37.

44. The method of claim 43, wherein the wound is an ulcer.

45. A method for treating or reversing renal and/or respiratory toxicity in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 29 or 37.

46. A method for treating a disorder resulting from elevated levels of COX-2 in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 29 or 37.

47. The method of claim 46, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, a skin-related condition, neoplasia, an inflammatory process in a disease, an ophthalmic disorder, pulmonary inflammation, a central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, a microbial infection, a cardiovascular disorder, a urinary disorder, a urological disorder, endothelial dysfunction, organ deterioration, tissue deterioration, or activation, adhesion and infiltration of neutrophils at the site of inflammation.

48. The method of claim 47, wherein the neoplasia is a brain cancer, a bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), a basal cell carcinoma, an adenocarcinoma, a gastrointestinal cancer, a lip cancer, a mouth cancer, an esophageal cancer, a small bowel cancer, a stomach cancer, a colon cancer, a liver cancer, a bladder cancer, a pancreas cancer, an ovary cancer, a cervical cancer, a lung cancer, a breast cancer, a skin cancer, a squamus cell cancer, a basal cell cancer, a prostate cancer, a renal cell carcinoma, a cancerous tumor, a growth, a polyp, an adenomatous polyp, a familial adenomatous polyposis or a fibrosis resulting from radiation therapy.

49. The method of claim 47, wherein the central nervous system disorder is cortical dementia, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, or central nervous system damage resulting from stroke, ischemia or trauma.

50. A method for inhibiting platelet aggregation in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 29 or 37.

51. A kit comprising at least one compound of claim 59.

52. The kit of claim 51, further comprising (i) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase; (ii) at least one therapeutic agent; or (iii) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and at least one therapeutic agent.

53. The kit of claim 52, wherein the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase; the at least one therapeutic agent; or the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and at least one therapeutic agent; are in the form of separate components in the kit

54. A kit comprising the composition of claim 14, 29 or 37.

55. A compound selected from the group consisting of :

1-(3-(1-(hydroxyimino)-4-(nitrooxy)butyl)-1- phenylpyrazol-5-yl-4-(methylsulfonyl)benzene;

1-(1-cyclohexyl-3-(1-(hydroxyimino)- 4-(nitroxy)butyl)pyrazol-5-yl)-4-(methylsulfonyl) benzene;

1-(3-(2-aza-2-methoxy-1-(3-(nitrooxy)propyl)vinyl- 1-cyclohexylpyrazol -5-yl)-4-(methylsulfonyl)benzene;

4-(3-(1-(hydroxyimino)-5-(nitrooxy)butyl)-4- (4-(methylsulfonyl)phenyl)-pyrazolyl) benzenecarbonitrile;

1-(1-cyclohexyl-3-(1-(hydroximino)- 6-(nitrooxy)hexyl)-pyrazol-5-yl)-4-(methylsulfonyl) benzene;

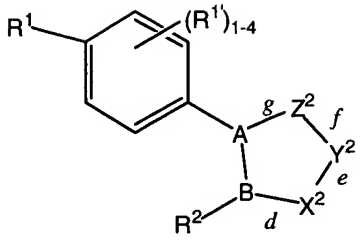
tert-butyl 2-((1E)-2-{1-cyclohexyl-5-[4-(methylsulfonyl)phenyl]pyrazol-3-yl}-5-(nitrooxy)-1-azapent-1-enyloxy)acetate; or a pharmaceutically acceptable salt thereof.

56. A composition comprising at least one compound of claim 55 and a pharmaceutically acceptable carrier.

57. The composition of claim 56, further comprising (i) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase; (ii) at least one therapeutic agent; or (iii) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and at least one therapeutic agent.

58. A kit comprising at least one compound of claim 55.

59. A compound of Formula (II), or a pharmaceutically acceptable salt thereof;



II

wherein:

A-B is:

(a) N-C;

(b) C-N; or

(c) N-N;

when sides *d* and *f* are double bonds, and sides *e* and *g* are single bonds, $-X^2-Y^2-Z^2-$ is:

(a) $=CR^4-CR^{4'}=CR^5-$;

(b) $=N-CR^4=CR^{4'}-$;

(c) $=N-CR^4=N-$;

(d) $=CR^4-N=CR^{4'}-$;

(e) $=CR^4-N=N-$;

(f) $=N-N=CR^4-$;

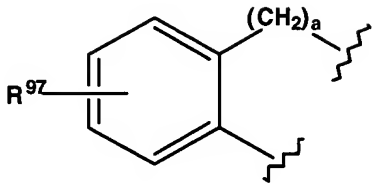
(g) $=N-N=N-$;

(h) $=CR^4-CR^5=N-$; or

(i) $=CR^{2'}-CR^5=N-$;

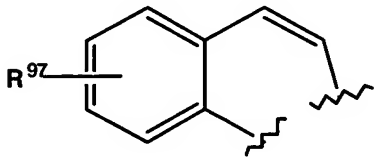
R^2 and $R^{2'}$, as defined herein taken together are:

(a)



or

(b)



or $R^{2'}$ and R^5, as defined herein, taken together with the carbon atoms to which they are attached are a cycloalkyl group or a heterocyclic ring;

R^{97} is:

(a) hydrogen;

(b) alkylthio;

(c) alkylsulfinyl;

(d) alkylsulfonyl;

(e) cyano;

(f) carboxyl;

(g) amino;

(h) lower alkyl;

(i) haloalkyl;

(j) hydroxy;

(k) alkoxy;

(l) haloalkoxy;

(m) alkylarylalkylamino;

(n) aminoalkyl;

(o) aminoaryl;

(p) sulfonamido;

(q) alkylsulfonamido;

(r) arylsulfonamido;

(s) heterocyclic ring;

(t) hydroxyalkyl; or

(u) nitro;

a is an integer from 1 to 3;

when sides *e* and *g* are double bonds, and sides *d* and *f* are single bonds, $-X^2-Y^2-Z^2-$ is:

(a) $-CR^4=N-N=$;

(b) $-N=N-CR^4=$;

(c) $-CR^4=N-CR^{4'}=$;

(d) $-N=CR^4-N=$;

(e) $-CR^4=CR^{4'}-N=$;

(f) $-N=CR^4-CR^5=$;

(g) $-CR^4=CR^5-CR^{5'}=$; or

(h) $-N=N-N=$;

when side *g* is a double bond, and sides *d*, *e* and *f* are single bonds, $-X^2-Y^2-Z^2-$ is:

(a) $-C(O)-O-CR^4=$;

(b) $-C(O)-NR^3-CR^4=$;

(c) $-C(O)-S-CR^4=$; or

(d) $-C(H)R^4-C(OH)R^5-N=$;

when sides *d* is a double bond, and sides *e*, *f* and *g* are single bonds, $-X^2-Y^2-Z^2-$ is:

(a) $=CR^4-O-C(O)-$;

(b) $=CR^4-NR^3-C(O)-$;

(c) $=CR^4-S-C(O)-$; or

(d) $=N-C(OH)R^4-C(H)R^5-$;

when sides *f* is a double bond, and sides *d*, *e* and *g* are single bonds, $-X^2-Y^2-Z^2-$ is:

(a) $-CH(R^4)-CR^5=N-$; or

(b) $-C(O)-CR^4=CR^5-$;

when sides *e* is a double bond, and sides *d*, *f* and *g* are single bonds,

$-X^2-Y^2-Z^2-$ is:

(a) $-N=CR^4-CH(R^5)-$; or

(b) $-CR^4=CR^5-C(O)-$;

when sides *d*, *e*, *f* and *g* are single bonds,

$-X^2-Y^2-Z^2-$ is:

(a) $-C(O)-CR^4(R^{4'})-C(O)-$;

R^1 is:

(a) $-S(O)_2-CH_3$;

(b) $-S(O)_2-NR^8(D^1)$;

(c) $-S(O)_2-N(D^1)-C(O)-CF_3$;

(d) $-S(O)-(NH)-NH(D^1)$;

(e) $-S(O)-(NH)-N(D^1)-C(O)-CF_3$;

(f) $-P(O)(CH_3)NH(D^1)$;

(g) $-P(O)(CH_3)_2$;

(h) $-C(S)-NH(D^1)$;

(i) $-S(O)(NH)CH_3$;

(j) $-P(O)(CH_3)OD^1$; or

(k) $-P(O)(CH_3)NH(D^1)$;

$R^{1'}$ at each occurrence is independently:

(a) hydrogen;

(b) halogen;

(c) methyl; or

(d) CH_2OH;

R^2 is:

(a) lower alkyl;

(b) cycloalkyl;

(c) mono-, di- or tri-substituted phenyl or naphthyl, wherein the substituents are each independently:

(1) hydrogen;

(2) halo;

(3) alkoxy;

(4) alkylthio;

(5) CN;

(6) haloalkyl, preferably CF_3;

(7) lower alkyl;

(8) N_3;

(9) $-CO_2D^1$;

(10) $-CO_2$-lower alkyl;

(11) $-(C(R^5)(R^6))_z-OD^1$;

(12) $-(C(R^5)(R^6))_z$-O-lower alkyl;

(13) lower alkyl-CO_2-R^5 ;

(14) $-OD^1$;

(15) haloalkoxy;

(16) amino;

(17) nitro;

(18) alkylsulfinyl; or

(19) heteroaryl;

(d) mono-, di- or tri-substituted heteroaryl, wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one heteroatom which is S, O, or N, and, optionally, 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one heteroatom which is N, and, optionally, 1, 2, 3, or 4 additional N atoms; wherein the substituents are each independently:

(1) hydrogen;

(2) halo;

(3) lower alkyl;

(4) alkoxy;

(5) alkylthio;

(6) CN;

(7) haloalkyl, preferably CF_3;

(8) N_3;

(9) $-C(R^5)(R^6)-OD^1$;

(10) $-C(R^5)(R^6)$-O-lower alkyl; or

(11) alkylsulfinyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

(f) $-NR^{10}R^{11}$;

(g) $-SR^{11}$;

(h) $-OR^{11}$;

(i) $-R^{11}$;

(j) alkenyl;

(k) alkynyl;

(l) unsubstituted, mono-, di-, tri- or tetra-substituted cycloalkenyl, wherein the substituents are each independently:

(1) halo;

(2) alkoxy;

(3) alkylthio;

(4) CN;

(5) haloalkyl, preferably CF_3;

(6) lower alkyl;

(7) N_3;

(8) $-CO_2D^1$;

(9) $-CO_2$-lower alkyl;

(10) $-C(R^{12})(R^{13})-OD^1$;

(11) $-C(R^{12})(R^{13})$-O-lower alkyl;

(12) lower alkyl-CO_2-R^{12} ;

(13) benzyloxy;

(14) -O-(lower alkyl)-CO_2R^{12};

(15) -O-(lower alkyl)-$NR^{12}R^{13}$; or

(16) alkylsulfinyl;

(m) mono-, di-, tri- or tetra-substituted heterocycloalkyl group of 5, 6 or 7 members, or a benzoheterocycle, wherein said heterocycloalkyl or benzoheterocycle contains 1 or 2 heteroatoms selected from O, S, or N and, optionally, contains a carbonyl group or a sulfonyl group, and wherein said substituents are each independently:

(1) halo;

(2) lower alkyl;

(3) alkoxy;

(4) alkylthio;

(5) CN;

(6) haloalkyl, preferably CF_3;

(7) N_3;

(8) $-C(R^{12})(R^{13})-OD^1$;

(9) $-C(R^{12})(R^{13})$-O-lower alkyl; or

(10) alkylsulfinyl;

(n) styryl, mono or di-substituted styryl, wherein the substituent are each independently:

(1) halo;

(2) alkoxy;

(3) alkylthio;

(4) CN;

(5) haloalkyl, preferably CF_3;

(6) lower alkyl;

(7) N_3;

(8) $-CO_2D^1$;

(9) $-CO_2$-lower alkyl;

(10) $-C(R^{12})(R^{13})-OD^1$;

(11) $-C(R^{12})(R^{13})$-O-lower alkyl;

(12) lower alkyl-CO_2-R^{12} ;

(13) benzyloxy;

(14) -O-(lower alkyl)-CO_2R^{12}; or

(15) -O-(lower alkyl)-$NR^{12}R^{13}$;

(o) phenylacetylene, mono- or di-substituted phenylacetylene, wherein the substituents are each independently:

(1) halo;

(2) alkoxy;

(3) alkylthio;

(4) CN;

(5) haloalkyl, preferably CF_3;

(6) lower alkyl;

(7) N_3;

(8) $-CO_2D^1$;

(9) $-CO_2$-lower alkyl;

(10) $-C(R^{12})(R^{13})-OD^1$;

(11) $-C(R^{12})(R^{13})$-O-lower alkyl;

(12) lower alkyl-CO_2-R^{12};

(13) benzyloxy;

(14) -O-(lower alkyl)-CO_2R^{12}; or

(15) -O-(lower alkyl)-$NR^{12}R^{13}$;

(p) fluoroalkenyl;

(q) mono- or di-substituted bicyclic heteroaryl of 8, 9 or 10 members, containing 2, 3, 4 or 5 heteroatoms, wherein at least one heteroatom resides on each ring of said bicyclic heteroaryl, said heteroatoms are each independently O, S and N and said substituents are each independently:

(1) hydrogen;

(2) halo;

(3) lower alkyl;

(4) alkoxy;

(5) alkylthio;

(6) CN;

(7) haloalkyl, preferably CF_3;

(8) N_3;

(9) $-C(R^5)(R^6)-OD^1$; or

(10) $-C(R^5)(R^6)$-O-lower alkyl;

(r) K;

(s) aryl;

(t) arylalkyl;

(u) cycloalkylalkyl;

(v) $-C(O)R^{11}$;

(u) hydrogen;

(v) arylalkenyl;

(w) arylalkoxy;

(x) alkoxy;

(y) aryloxy;

(z) cycloalkoxy;

(aa) arylthio;

(bb) alkylthio;

(cc) arylalkylthio; or

(dd) cycloalkylthio;

R^3 is:

(a) hydrogen;

(b) haloalkyl, preferably CF_3;

(c) CN;

(d) lower alkyl;

(e) $-(C(R_e)(R_f))_p$-U-V;

(f) K;

(g) unsubstituted or substituted:

(1) lower alkyl-Q;

(2) lower alkyl-O- lower alkyl-Q;

(3) lower alkyl-S-lower alkyl-Q;

(4) lower alkyl-O-Q;

(5) lower alkyl-S-Q;

(6) lower alkyl-O-V;

(7) lower alkyl-S-V;

(8) lower alkyl-O-K; or

(9) lower alkyl-S-K;

wherein the substituent(s) reside on the lower alkyl group;

(h) Q;

(i) alkylcarbonyl;

(j) arylcarbonyl;

(k) alkylarylcarbonyl;

(l) arylalkylcarbonyl;

(m) carboxylic ester;

(n) carboxamido;

(o) cycloalkyl;

(p) mono-, di- or tri-substituted phenyl or naphthyl, wherein the substituents are each independently:

(1) hydrogen;

(2) halo;

(3) alkoxy;

(4) alkylthio;

(5) CN;

(6) haloalkyl, preferably CF_3;

(7) lower alkyl;

(8) N_3;

(9) $-CO_2D^1$;

(10) $-CO_2$-lower alkyl;

(11) $-(C(R^5)(R^6))_z-OD^1$;

(12) $-(C(R^5)(R^6))_z$-O-lower alkyl;

(13) lower alkyl-CO_2-R^5 ;

(14) $-OD^1$;

(15) haloalkoxy;

(16) amino;

(17) nitro; or

(18) alkylsulfinyl;

(q) alkenyl;

(r) alkynyl;

(s) arylalkyl;

(t) lower alkyl-OD^1;

(u) alkoxyalkyl;

(v) aminoalkyl;

(w) lower alkyl-CO_2R^{10};

(x) lower alkyl-$C(O)NR^{10}(R^{10'})$;

(y) heterocyclicalkyl; or

(z) heterocyclic ring-C(O)-;

R^4, $R^{4'}$, R^5 and $R^{5'}$ are each independently:

(a) hydrogen;

(b) amino;

(c) CN;

(d) lower alkyl;

(e) haloalkyl;

(f) alkoxy;

(g) alkylthio;

(h) Q;

(i) -O-Q;

(j) -S-Q;

(k) K;

(l) cycloalkoxy;

(m) cycloalkylthio;

(n) unsubstituted, mono-, or di-substituted phenyl or unsubstituted, mono-, or di-substituted benzyl, wherein the substituents are each independently:

(1) halo;

(2) lower alkyl;

(3) alkoxy;

(4) alkylthio;

(5) CN;

(6) haloalkyl, preferably CF_3;

(7) N_3;

(8) Q;

(9) nitro; or

(10) amino;

(o) unsubstituted, mono-, or di-substituted heteroaryl or unsubstituted, mono-, or di-substituted heteroarylmethyl, wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one heteroatom which is S, O, or N, and, optionally, 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one heteroatom which is N, and, optionally, 1, 2, 3, or 4 additional N atoms; said substituents are each independently:

(1) halo;

(2) lower alkyl;

(3) alkoxy;

(4) alkylthio;

(5) CN;

(6) haloalkyl, preferably CF_3;

(7) N_3;

(8) $-C(R^6)(R^7)-OD^1$;

(9) $-C(R^6)(R^7)$-O-lower alkyl; or

(10) alkylsulfinyl

(p) $-CON(R^8)(R^8)$;

(q) $-CH_2OR^8$;

(r) $-CH_2OCN$;

(s) unsubstituted or substituted:

(1) lower alkyl-Q;

(2) -O-lower alkyl-Q;

(3) -S-lower alkyl-Q;

(4) lower alkyl-O-lower alkyl-Q;

(5) lower alkyl-S-lower alkyl-Q;

(6) lower alkyl-O-Q;

(7) lower alkyl-S-Q;

(8) lower alkyl-O-K;

(9) lower alkyl-S-K;

(10) lower alkyl-O-V; or

(11) lower alkyl-S-V;

wherein the substituent(s) resides on the lower alkyl;

(t) cycloalkyl;

(u) aryl;

(v) arylalkyl;

(w) cycloalkylalkyl;

(x) aryloxy;

(y) arylalkoxy;

(z) arylalkylthio;

(aa) cycloalkylalkoxy;

(bb) heterocycloalkyl;

(cc) alkylsulfonyloxy;

(dd) alkylsulfonyl;

(ee) arylsulfonyl;

(ff) arylsulfonyloxy;

(gg) $-C(O)R^{10}$;

(hh) nitro;

(ii) amino;

(jj) aminoalkyl;

(kk) -C(O)-alkyl-heterocyclic ring;

(ll) halo;

(mm) heterocyclic ring;

(nn) $-CO_2D^1$;

(oo) carboxyl;

(pp) amidyl; or

(qq) alkoxyalkyl;

alternatively, R^4 and R^5 together with the carbons to which they are attached are:

(a) cycloalkyl;

(b) aryl; or

(c) heterocyclic ring;

alternatively, R^4 and $R^{4'}$ or R^5 and $R^{5'}$ taken together with the carbon to which they are attached are:

(a) cycloalkyl; or

(b) heterocyclic ring;

alternatively, R^4 and R^5, $R^{4'}$ and $R^{5'}$, R^4 and $R^{5'}$, or $R^{4'}$ and R^5 when substituents on adjacent carbon atoms taken together with the carbons to which they are attached are:

(a) cycloalkyl;

(b) heterocyclic ring; or

(c) aryl;

R^6 and R^7 are each independently:

(a) hydrogen;

(b) unsubstituted, mono- or di-substituted phenyl; unsubstituted, mono- or di-substituted benzyl; unsubstituted, mono- or di-substituted heteroaryl; mono- or di-substituted heteroarylmethyl, wherein said substituents are each independently:

(1) halo;

(2) lower alkyl;

(3) alkoxy;

(4) alkylthio;

(5) CN;

(6) haloalkyl, preferably CF_3;

(7) N_3;

(8) $-C(R^{14})(R^{15})-OD^1$; or

(9) $-C(R^{14})(R^{15})$-O-lower alkyl;

(c) lower alkyl;

(d) $-CH_2OR^8$;

(e) CN;

(f) $-CH_2CN$;

(g) haloalkyl, preferably fluoroalkyl;

(h) $-CON(R^8)(R^8)$;

(i) halo; or

(j) $-OR^8$;

R^8 is:

(a) hydrogen;

(b) K; or

(c) R^9 ;

alternatively, R^5 and $R^{5'}$, R^6 and R^7 or R^7 and R^8 together with the carbon to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6 or 7 atoms; optionally containing up to two heteroatoms selected from oxygen, $S(O)_o$ or NR_i;

R^9 is:

(a) lower alkyl;

(b) lower alkyl-CO_2D^1;

(c) lower alkyl-NHD^1;

(d) phenyl or mono-, di- or tri-substituted phenyl, wherein the substituents are each independently:

(1) halo;

(2) lower alkyl;

(3) alkoxy;

(4) alkylthio;

(5) lower alkyl-CO_2D^1;

(6) lower alkyl-NHD^1;

(7) CN;

(8) CO_2D^1; or

(9) haloalkyl, preferably fluoroalkyl;

(e) benzyl, mono-, di- or tri-substituted benzyl, wherein the substituents are each independently:

(1) halo;

(2) lower alkyl;

(3) alkoxy;

(4) alkylthio;

(5) lower alkyl-CO_2D^1;

(6) lower alkyl-NHD^1;

(7) CN;

(8) -CO_2D^1; or

(9) haloalkyl, preferably CF_3;

(f) cycloalkyl;

(g) K; or

(h) benzoyl, mono-, di-, or trisubstituted benzoyl, wherein the substituents are each independently:

(1) halo;

(2) lower alkyl;

(3) alkoxy;

(4) alkylthio;

(5) lower alkyl-CO_2D^1;

(6) lower alkyl-NHD^1;

(7) CN;

(8) -CO_2D^1; or

(9) haloalkyl, preferably CF_3;

R^{10} and $R^{10'}$ are each independently:

(a) hydrogen; or

(b) R^{11};

R^{11} is:

(a) lower alkyl;

(b) cycloalkyl;

(c) unsubstituted, mono-, di- or tri-substituted phenyl or naphthyl, wherein the substituents are each independently:

(1) halo;

(2) alkoxy;

(3) alkylthio;

(4) CN;

(5) haloalkyl, preferably CF_3;

(6) lower alkyl;

(7) N_3;

(8) $-CO_2D^1$;

(9) $-CO_2$-lower alkyl;

(10) $-C(R^{12})(R^{13})-OD^1$;

(11) $-C(R^{12})(R^{13})$-O-lower alkyl;

(12) lower alkyl-CO_2D^1;

(13) lower alkyl-CO_2R^{12};

(14) benzyloxy;

(15) -O-(lower alkyl)-CO_2D^1;

(16) -O-(lower alkyl)-CO_2R^{12}; or

(17) -O-(lower alkyl)-$NR^{12}R^{13}$;

(d) unsubstituted, mono-, di- or tri-substituted heteroaryl, wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one heteroatom which is S, O, or N, and, optionally, 1, 2, or 3 additional N atoms; or said heteroaryl is a monocyclic ring of 6 atoms, said ring having one heteroatom which is N, and, optionally 1, 2, or 3 additional N atoms, and wherein said substituents are each independently:

(1) halo;

(2) lower alkyl;

(3) alkoxy;

(4) alkylthio;

(5) CN;

(6) haloalkyl, preferably CF_3;

(7) N_3;

(8) $-C(R^{12})(R^{13})-OD^1$; or

(9) $-C(R^{12})(R^{13})$-O-lower alkyl;

(e) unsubstituted, mono- or di-substituted benzoheterocycle, wherein the benzoheterocycle is a 5, 6, or 7-membered ring which contains 1 or 2 heteroatoms independently selected from O, S, or N, and, optionally, a carbonyl group or a sulfonyl group, wherein said substituents are each independently:

(1) halo;

(2) lower alkyl;

(3) alkoxy;

(4) alkylthio;

(5) CN;

(6) haloalkyl, preferably CF_3;

(7) N_3;

(8) $-C(R^{12})(R^{13})-OD^1$; or

(9) $-C(R^{12})(R^{13})$-O-lower alkyl;

(f) unsubstituted, mono- or di-substituted benzocarbocycle, wherein the carbocycle is a 5, 6, or 7-membered ring which optionally contains a carbonyl group, wherein said substituents are each independently :

(1) halo;

(2) lower alkyl;

(3) alkoxy;

(4) alkylthio;

(5) CN;

(6) haloalkyl, preferably CF_3;

(7) N_3;

(8) $-C(R^{12})(R^{13})-OD^1$; or

(9) $-C(R^{12})(R^{13})$-O-lower alkyl;

(g) hydrogen; or

(h) K

R^{12} and R^{13} are each independently:

(a) hydrogen;

(b) lower alkyl; or

(c) aryl; or

R^{12} and R^{13} together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6 or 7 atoms;

R^{14} and R^{15} are each independently :

(a) hydrogen; or

(b) lower alkyl; or

R^{14} and R^{15} together with the atom to which they are attached form a carbonyl, a thial, or a saturated monocyclic ring of 3, 4, 5, 6 or 7 atoms;

D^1 is:

(a) hydrogen or

(b) D;

D is:

(a) V; or

(b) K;

U is:

(a) oxygen;

(b) sulfur; or

(c) $-N(R_a)(R_i)-$;

V is:

(a) -NO;

(b) $-NO_2$; or

(c) hydrogen

K is $-W_{aa}-E_b-(C(R_e)(R_f))_p-E_c-(C(R_e)(R_f))_x-W_d-(C(R_e)(R_f))_y-W_i-E_j-W_g-(C(R_e)(R_f))_z-U-V$; wherein aa, b, c, d, g, i and j are each independently an integer from 0 to 3;

p, x, y and z are each independently an integer from 0 to 10;

W at each occurrence is independently:

(a) -C(O)-;

(b) -C(S)-;

(c) -T-;

(d) $-(C(R_e)(R_f))_h-$;

(e) alkyl;

(f) aryl;

(g) heterocyclic ring;

(h) arylheterocyclic ring, or

(i) $-(CH_2CH_2O)_q-$;

E at each occurrence is independently:

(a) -T-;

(b) alkyl;

(c) aryl;

(d) $-(C(R_e)(R_f))_h-$;

(e) heterocyclic ring;

(f) arylheterocyclic ring; or

(g) $-(CH_2CH_2O)_q-$;

h is an integer form 1 to 10;

q is an integer from 1 to 5;

R_e and R_f are each independently:

(a) hydrogen;

(b) alkyl;

(c) cycloalkoxy;

(d) halogen;

(e) hydroxy;

(f) hydroxyalkyl;

(g) alkoxyalkyl;

(h) arylheterocyclic ring;

(i) cycloalkylalkyl;

(j) heterocyclicalkyl;

(k) alkoxy;

(l) haloalkoxy;

(m) amino;

(n) alkylamino;

(o) dialkylamino;

(p) arylamino;

(q) diarylamino;

(r) alkylarylamino;

(s) alkoxyhaloalkyl;

(t) haloalkoxy;

(u) sulfonic acid;

(v) alkylsulfonic acid;

(w) arylsulfonic acid;

(x) arylalkoxy;

(y) alkylthio;

(z) arylthio;

(aa) cyano;

(bb) aminoalkyl;

(cc) aminoaryl;

(dd) alkoxy;

(ee) aryl;

(ff) arylalkyl;

(gg) carboxamido;

(hh) alkylcarboxamido;

(ii) arylcarboxamido;

(jj) amidyl;

(kk) carboxyl;

(ll) carbamoyl;

(mm) alkylcarboxylic acid;

(nn) arylcarboxylic acid;

(oo) alkylcarbonyl;

(pp) arylcarbonyl;

(qq) ester;

(rr) carboxylic ester;

(ss) alkylcarboxylic ester;

(tt) arylcarboxylic ester;

(uu) haloalkoxy;

(vv) sulfonamido;

(ww) alkylsulfonamido;

(xx) arylsulfonamido;

(yy) alkylsulfonyl,

(zz) alkylsulfonyloxy,

(aaa) arylsulfonyl,

(bbb) arylsulphonyloxy

(ccc) sulfonic ester;

(ddd) carbamoyl;

(eee) urea;

(fff) nitro;

(ggg) -U-V; or

(hhh) $-(C(R'_e)(R'_f))_k$-U-V or

R_e and R_f taken together are:

(a) oxo;

(b) thial;

(c) oxime; or

(d) hydrazone;

R_e and R_f taken together with the carbon atom to which they are attached are:

(a) heterocyclic ring;

(b) cycloalkyl group; or

(c) bridged cycloalkyl group;

R'_e and R'_f are each independently selected from R_e;

k is an integer from 1 to 3;

T at each occurrence is independently:

(a) a covalent bond,

(b) carbonyl,

(c) an oxygen,

(d) $-S(O)_o-$; or

(e) $-N(R_a)(R_i)-$;

o is an integer from 0 to 2;

Q is:

(a) $-C(O)-U-D^1$;

(b) $-CO_2$-lower alkyl;

(c) tetrazolyl-5-yl;

(d) $-C(R^7)(R^8)(S-D^1)$;

(e) $-C(R^7)(R^8)(O-D^1)$; or

(f) $-C(R^7)(R^8)$(O-lower alkyl);

R_a is:

(a) a lone pair of electron;

(b) hydrogen; or

(c) lower alkyl;

R_i is:

(a) hydrogen;

(b) alkyl;

(c) aryl;

(d) alkylcarboxylic acid;

(e) arylcarboxylic acid;

(f) alkylcarboxylic ester;

(g) arylcarboxylic ester;

(h) alkylcarboxamido;

(i) arylcarboxamido;

(j) alkylsulfinyl;

(k) alkylsulfonyl;

(l) alkylsulfonyloxy,

(m) arylsulfinyl;

(n) arylsulfonyl;

(o) arylsulphonyloxy;

(p) sulfonamido;

(q) carboxamido;

(r) carboxylic ester;

(s) aminoalkyl;

(t) aminoaryl;

(u) $-CH_2-C(U-V)(R_e)(R_f)$;

(v) a bond to an adjacent atom creating a double bond to that atom; or

(w) $-(N_2O_2-)^-\bullet M^+$, wherein M^+ is an organic or inorganic cation;

with the proviso that the compound of Formula (II) must contain at least one oxime group and/or hydrazone group.